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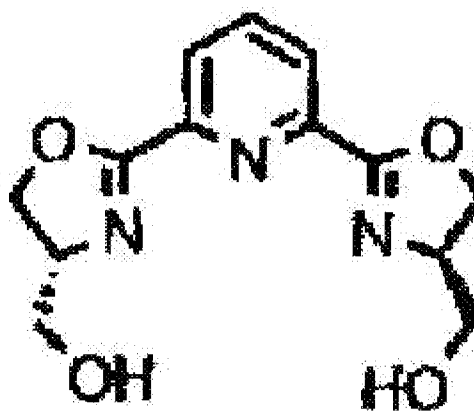
(72)Inventor : KOBAYASHI OSAMU

(54) CHIRAL RARE EARTH METALLIC CATALYST AND ASYMMETRIC ALDOL REACTION PROCESS

(57)Abstract:

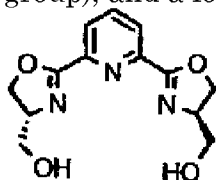
PROBLEM TO BE SOLVED: To provide a new asymmetric synthesis catalyst which shown high yield and optical selectivity and also has general-purpose properties with an advantage of executing its simple operation for reaction as well as an asymmetric synthesizing process using this catalyst.

SOLUTION: The rare earth metallic catalyst contains a rare earth metallic compound represented by formula (I): $M(OR_f)_3$ (wherein M is at least one kind of rare earth elements and R_f is an alkylsulfonyl group containing fluorine) and a chiral pyridinebisoxazoline compound of a skeleton represented by formula (II): The asymmetric aldol reaction process uses this catalyst.



[Claim 1]A rare earth metal compound expressed with following formula $M(OR_f)_3$ (M shows at least one sort of a rare earth element, and R_f shows a fluorine-containing alkyl sulfonyl

group), and a following formula [Formula 1]



The chiral rare earth metal catalyst coming out and containing the chiral pyridine-oxazoline compound of the skeleton expressed.

[Claim 2] A chiral rare earth metal catalyst of claim 1 in which a rare earth element contains all from Sc to Lu.

[Claim 3] A manufacturing method of a chiral rare earth metal catalyst being a manufacturing method of a catalyst of claim 1 or 2, mixing a rare earth metal compound and a chiral pyridine-oxazoline compound in a polar solvent, and removing a polar solvent subsequently.

[Claim 4] A dissymmetry aldol reaction method which is a dissymmetry aldol reaction method using a catalyst of claim 1 or 2, and is characterized by making a silyl-enol-ether compound of an aldehyde-reaction thing react, and compounding a hydroxyketone compound the bottom of existence of said catalyst, and in a hydrous solvent.

[Claim 5] A dissymmetry aldol reaction method of claim 4 with which a hydrous solvent consists of water and alcohol.

DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001]

[Field of the Invention] The invention of this application relates to a chiral rare earth metal catalyst and a dissymmetry aldol reaction method. In more detail, the invention of this application has the Lewis acid catalyst function, and relates to a new chiral rare earth metal catalyst useful as an asymmetric-synthesis catalyst, and the dissymmetry aldol reaction method using this.

[0002]

[The technical problem of a Prior art and an invention] In recent years, in the chemosynthesis in many fields, such as drugs and perfume, realization of the asymmetric synthesis which was excellent in optical selectivity with high yield has been an important technical problem. In particular, in the asymmetric synthesis reaction, the method of performing using a catalyst is just going to attract attention.

[0003] Although the thing which made the metallic element configure a chiral ligand compound was proposed as such a catalyst until now, the reaction to which these conventional chiral catalysts are applied was limited considerably, and it was made into the technical problem for the restrictions of the operation top of a reaction condition etc. to be also large.

[0004] On the other hand taking advantage of the characteristic that a characteristic rare earth metal compound exists stably in underwater and the artificers of this application have a function as Lewis acid, this is made into a catalyst, It found out that a fundamental and important carbon-carbon bonding formation reaction advanced smoothly in hydrous solvents including water on

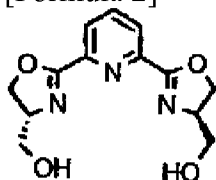
organic synthesis, such as an aldol reaction and a Diels-Alder reaction, and the new catalyst system and synthetic reaction based on this are proposed.

[0005]Then, the invention of this application is based also on the knowledge by the artificers of this application as above, and a new proposal, It is making into the technical problem to provide the new asymmetric-synthesis catalyst whose simple reaction operation cancel the problem about the conventional asymmetric synthesis, and yield and optical selectivity are also high, are flexible, and is moreover made possible, and the asymmetric synthesis method using this.

[0006]

[Means for Solving the Problem]A rare earth metal compound expressed with following formula $M(OR_f)_3$ (M shows at least one sort of a rare earth element, and R_f shows a fluorine-containing alkyl sulfonyl group) to the 1st as that in which an invention of this application solves a technical problem as above-mentioned, and a following formula [0007]

[Formula 2]



[0008]Providing the chiral rare earth metal catalyst coming out and containing the chiral pyridinescrew oxazoline compound of the skeleton expressed, a rare earth element provides the 2nd with said chiral rare earth metal catalyst which is one of the sorts from Sc to Lu.

[0009]An invention of this application is a manufacturing method of said catalyst, in a polar solvent, mixes a rare earth metal compound and a chiral pyridine oxazoline compound, and provides the 3rd with a manufacturing method of a chiral rare earth metal catalyst removing a polar solvent subsequently.

[0010]An invention of this application is a dissymmetry aldol reaction method which uses said catalyst for the 4th, and it is the bottom of existence of said catalyst, and under [hydrous solvent] setting, A dissymmetry aldol reaction method making a silyl-enol-ether compound of an aldehyde-reaction thing react, and compounding a hydroxyketone compound is provided, and the 5th is provided with a dissymmetry aldol reaction method with which a hydrous solvent consists of water and alcohol.

[0011]

[Embodiment of the Invention]Although the invention of this application has the feature as above-mentioned, it describes that embodiment below.

[0012]First, although the chiral rare earth metal catalyst of an invention of this application is fundamentally constituted by a rare earth metal compound and the chiral pyridinescrew oxazoline compound as aforementioned, The rare earth metal compounds of these may be various kinds of things of rare earth element fluorine-containing ARUMORU sulfonate, such as yttrium and a lanthanide system.

[0013]As a rare earth element, Yb (ytterbium), Y (yttrium), Dy (dysprosium), Nd (neodmium), etc. are especially shown as an example of a suitable thing. The fluorine-containing alkyl sulfonyl group which combines these rare earth elements, Some or all of a hydrogen atom of an alkyl group is replaced by the fluorine atom, and the perfluoroalkyl group of F_{2n} of $-SO_2-C_{n+1}$ ($n \leq 10$) is especially illustrated as a suitable thing. A triflate group is one of the typical thing.

[0014]The aforementioned chiral pyridinescrew oxazoline compound may have suitably various kinds of substituents which do not check chiral catalyst activity to each of the pyridine ring and

an oxazoline ring, for example, a hydrocarbon group, an alkoxy group and an amino group, a heterocycle group, etc. The hydrogen atom of the hydroxyl of -CH₂-OH combined with the oxazoline ring may be replaced by an alkoxy group, an acyl group, sulfonyl group, etc.

[0015]The chiral rare earth metal catalyst of this invention containing the above rare earth metal compound and a chiral pyridinescrew oxazoline compound can be prepared by mixing that each in a polar solvent and subsequently removing a solvent.

[0016]As a polar solvent, various kinds of things, such as nitril, sulfoxides, and acid, may be used. Preparation can be performed, for example on temperature conditions (-10 ** - about 10 **).

[0017]About the amount of a rare earth metal compound and the chiral pyridinescrew oxazoline compound used, it can prepare at a rate of 0.1-10 mol to 1 mol of rare earth metal compounds using the chiral pyridinescrew oxazoline compound as a ligand.

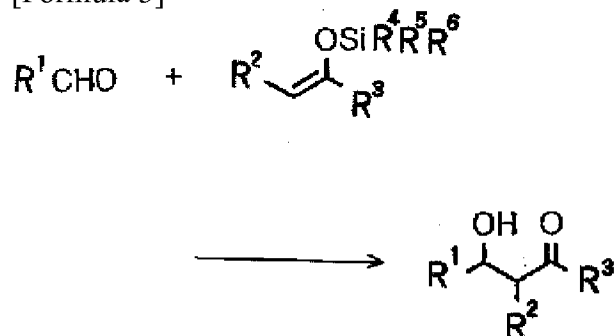
[0018]The chiral rare earth metal catalyst of an invention of this prepared application has the Lewes acidity, enables formation of the carbon-carbon bonding as foundations of organic synthesis, and, moreover, makes an asymmetric synthesis possible.

[0019]The invention of this application provides a dissymmetry aldol reaction method concretely as one of such the asymmetric syntheses. That is, in this invention, under existence of the catalyst as aforementioned, an aldehyde compound and a silyl-enol-ether compound are made to react into a hydrous solvent, and the asymmetric synthesis of the hydroxyketone compound is made possible.

[0020]The asymmetric synthesis of this hydroxyketone compound can be illustrated, for example as a following reaction formula.

[0021]

[Formula 3]



[0022]R¹, R², and R³ in a formula, A hydrocarbon group united via heteroatoms, such as a hydrocarbon group which may have a substituent or an oxygen atom, and a sulfur atom, which may have a substituent is shown, and R⁴, R⁵, and R⁶ show a hydrocarbon group respectively.

[0023]In this reaction, although a hydrous solvent is used, as this hydrous solvent, it is used as mixing with water or water, alcohol, for example, aliphatic series, alicyclic alcohol, or THF. A mixed solvent of water and alcohol is used suitably and it is [a rate of water in this case] preferred to use 0.9 or less as a capacity factor to alcohol.

[0024]The amount of the aforementioned catalyst used for a reaction can be made into about 4-40 mol %, for example about each of a rare earth metal compound and a chiral pyridinescrew oxazoline compound. The amount of an aldehyde compound and silyl-enol-ether compound used may be about 1 / ten to 10/1 as a mole ratio.

[0025]Mild conditions can be used for temperature of a reaction. For example, it is a temperature

requirement (-5 ** - 15 **).

[0026]In a dissymmetry aldol reaction method of this above invention, also in an environmental aspect, it can use an advantageous hydrous solvent, and reaction operation is not only simple, but has an advantage on composition of not needing very low temperature moreover. And yield and an asymmetric yield are also good.

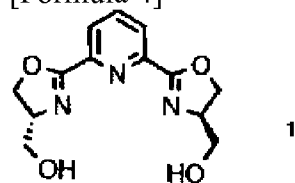
[0027]Then, an example is shown below and an invention of this application is explained to it in more detail. Of course, an invention is not limited by the following examples.

[0028]

[Example]Ytterbium (m) Tori Flatow dried by 200 ** / 1mmHg under <Example 1> argon atmosphere for 1 hour (0.04 mmol) pyridinescrew oxazoline CH₂ OH (1 -- 0.048 mmol) expressed with a following formula by 20-mol% of the acetonitrile (0.8 ml) solution 24-mol% was added at 0 **, it stirred for 1 hour, and the chiral ytterbium catalyst was prepared by distilling off acetonitrile and drying under decompression.

[0029]

[Formula 4]



[0030]Then, benzaldehyde (0.2mmol) and the H₂O-EtOH (1:9, a total of 1.0 ml) mixed solution of the 1-phenyl-1-trimethylsiloxy 1-propene (0.3mmol) were added on 0 ** conditions into this. After having added saturation NaHCO₃ solution (7 ml) after stirring for 24 hours, and separating an organic layer, the methylene chloride (10mlx2) extracted output from the water layer. The place which distilled off the bottom solvent of decompression and generated the residue with silica gel thin layer chromatography after drying an organic layer with anhydrous sodium sulfate, 1,3-diphenyl-3-hydroxy-2-methyl-1-propanone was obtained (93% of yield, syn:anti=72:83, 35%ee (syn)).

[0031]The ratio of diastereomer was determined from proton NMR. The optical purity of a Syn object is an optical isomer isolation column (Daicel Chemical Industries make:). [CHIRALPAK AD and] Hexane/2-propanol = the HPLC analysis using 30/1, retention time 17.88, 22.64min (syn), 32.54, and 36.54min (anti) determined.

[0032]The identification property value of output is as in the following table.

[0033]

[Table 1]

1,3-Diphenyl-3-hydroxy-2-methyl-1-propanone: (syn/anti = 72/28)

¹H NMR (CDCl₃) δ 1.05 (d, 0.84H, J = 7.2 Hz), 1.19 (d, 2.16H, J = 7.2 Hz), 3.10 (brs, 1H), 3.66-3.89 (m, 1H), 4.98 (d, 0.28H, J = 8.1 Hz), 5.22 (d, 0.72H, J = 3.1 Hz), 7.22-7.58 (m, 8H), 7.90-7.97 (m, 2H).

¹³C NMR (CDCl₃) δ 11.2, 15.6, 47.0, 47.9, 73.1, 76.7, 126.0, 126.7, 127.2, 127.8, 128.2, 128.3, 128.40, 128.44, 128.6, 128.7, 133.2, 133.5, 135.6, 136.7, 141.8, 142.2, 204.8, 205.6.

IR (neat) 3467, 1678 cm⁻¹.

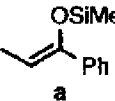
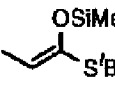
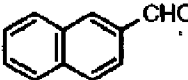
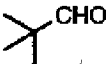


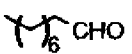
HPLC (Daicel Chiralcel AD, hexane/*i*-PrOH = 30/1, flow rate = 1.0 mL/min). *t*_R = 17.88 min (minor), *t*_R = 22.64 min (major) (syn), *t*_R = 32.54 min (minor), *t*_R = 36.54 min (major) (anti).

[0034]The dissymmetry aldol reaction with another aldehyde compound or a eno rate compound was performed like <Example 2> example 1.

[0035]The result was shown in the following table.

[0036]

[Table 2]

$R^1CHO + R^2\text{---}\text{CH}=\text{CH}\text{---}R^3 \xrightarrow[\substack{H_2O/EtOH = 1/9 \\ 0^\circ C, 24 h}]{\substack{Yb(OTf)_3 (20 \text{ mol}\%) \\ \text{Ligand} (24 \text{ mol}\%)}} R^1\text{---}\text{CH}(\text{OH})\text{---}\text{CH}(R^2)\text{---}C(=O)R^3$					
Run	Aldehyde	Enolate	Yield (%)	Syn/Anti	Ee (Syn/Anti)
1	PhCHO		93	72/28	35/10
2	PhCHO		49	85/15	30/14
3		a	60	72/28	25/5
4		a	23	50/50	23/11
5		a	59	70/30	44/17
6		a	50	62/38	45/10
7		a	63	61/39	55/2

[0037]The identification property value of a resultant is as in the following table.

[0038]

[Table 3]

S-tert-Butyl 3-hydroxy-2-methyl-3-phenylpropanethioate: (*syn/anti* = 85/15)

¹H NMR (CDCl₃) δ 1.01 (d, 0.45H, *J* = 7.1 Hz), 1.13 (d, 2.55H, *J* = 7.1 Hz), 1.43 (s, 7.65H), 1.46 (s, 1.35H), 2.77-2.85 (m, 0.85H), 2.85-2.92 (m, 0.15H), 4.77 (d, 0.15H, *J* = 8.1 Hz), 5.07 (d, 0.85H, *J* = 3.9 Hz), 7.21-7.39 (m, 5H).

¹³C NMR (CDCl₃) δ 11.4, 15.5, 29.6, 29.7, 48.2, 55.0, 55.5, 73.8, 126.1, 126.6, 127.4, 128.0, 128.2, 128.4, 141.2, 205.1.

HPLC (Daicel Chiralcel OJ, hexane/*i*-PrOH = 30/1, flow rate = 1.0 mL/min). *t*_R = 6.41 min (major), *t*_R = 7.02 min (minor) (*syn*), *t*_R = 7.75 min (major), *t*_R = 8.91 min (minor) (*anti*).

3-Hydroxy-2-methyl-3-(2-naphthyl)-1-phenyl-1-propanone: (*syn/anti* = 72/28)

syn:

¹H NMR (CDCl₃) δ 1.20 (d, 3H, *J* = 7.2 Hz), 3.03 (brs, 1H), 3.80 (dq, 1H, *J* = 2.9, 4.4 Hz), 5.42 (d, 1H, *J* = 2.7 Hz), 7.54-7.62 (m, 6H), 7.81-8.02 (m, 6H).

¹³C NMR (CDCl₃) δ 15.8, 47.8, 76.9, 124.0, 125.9, 126.0, 126.2, 127.7, 128.0, 128.4, 128.6, 128.8, 133.11, 133.14, 133.3, 136.7, 139.5, 204.9.

anti:

¹H NMR (CDCl₃) δ 1.02 (d, 3H, *J* = 7.3 Hz), 3.03 (brs, 1H), 3.87 (dq, 1H, *J* = 7.4 Hz), 5.09 (d, 1H, *J* = 7.8 Hz), 7.38-7.52 (m, 6H), 7.74-7.80 (m, 46H), 7.92-7.94 (m, 2H).

¹³C NMR (CDCl₃) δ 11.2, 46.8, 73.1, 124.0, 124.9, 125.7, 126.0, 127.6, 127.9, 128.0, 128.4, 128.7, 132.7, 133.2, 133.5, 135.5, 139.2, 205.7.

HPLC (Daicel Chiralcel AD, hexane/*i*-PrOH = 30/1, flow rate = 1.0 mL/min). *t*_R = 32.19 min (minor), *t*_R = 36.06 min (major) (*syn*), *t*_R = 32.51 min (minor), *t*_R = 36.16 min (major) (*anti*).

[0039]

[Table 4]

3-Hydroxy-1-phenyl-2,4,4-trimethyl-1-pentanone: (*syn/anti* = 50/50)

syn:

¹H NMR (CDCl₃) δ 0.07 (s, 9H), 1.00 (brs, 1H), 1.45 (d, 3H, *J* = 7.0 Hz), 3.42 (d, 1H, *J* = 1.78 Hz), 3.8 (dq, 1H, *J* = 1.7, 5.4 Hz), 7.51 (t, 2H, *J* = 7.8 Hz), 7.59-7.64 (m, 1H), 7.95-7.97 (m, 2H).

¹³C NMR (CDCl₃) δ 19.1, 26.1, 36.4, 37.6, 85.1, 128.3, 129.0, 133.7, 162.7, 206.3.

HPLC (Daicel Chiralcel AD, hexane/*i*-PrOH = 90/1, flow rate = 1.0 mL/min). *t*_R = 16.32 min (minor), *t*_R = 21.31 min (major) (*syn*), *t*_R = 9.48 min (minor), *t*_R = 11.99 min (major) (*anti*).

2,4-Dimethyl-3-hydroxy-1-phenyl-1-pentanone: (*syn/anti* = 70/30)

¹H NMR (CDCl₃) δ 0.84-1.04 (m, 6H), 1.10-1.28 (m, 3H), 1.64-1.81 (m, 1H), 2.99 (brs, 1H), 3.48-3.68 (m, 1H), 7.38-7.47 (m, 2H), 7.48-7.56 (m, 1H), 7.85-7.93 (m, 2H).

¹³C NMR (CDCl₃) δ 10.7, 16.0, 17.0, 19.0, 19.1, 20.0, 30.7, 31.3, 41.8, 42.4, 128.3, 128.4, 128.7, 128.8, 133.4, 205.9, 206.3.

HPLC (Daicel Chiralcel AD, hexane/*i*-PrOH = 90/1, flow rate = 1.0 mL/min). *t*_R = 29.22 min (major), *t*_R = 33.47 min (minor) (*syn*), *t*_R = 30.99 min (minor), *t*_R = 33.50 min (major) (*anti*).

[0040]

[Table 5]

2,5-Dimethyl-3-hydroxy-1-phenyl-1-hexanone: (*syn/anti* = 62/38)

syn:

¹H NMR (CDCl₃) δ 0.90-0.95 (m, 6H), 1.26 (d, 3H, *J* = 7.3 Hz), 1.54-1.61 (m, 1H), 1.80-1.94 (m, 1H), 3.39-3.45 (m, 1H), 3.02 (brs, 1H), 4.12-4.16 (m, 1H), 7.46-7.54 (m, 2H), 7.56-7.62 (m, 1H), 7.94-7.97 (m, 2H).

¹³C NMR (CDCl₃) δ 11.1, 22.0, 23.5, 24.6, 43.4, 44.9, 128.4, 128.8, 133.4, 135.9, 206.0.

HPLC (Daicel Chiralcel AD, hexane/*i*-PrOH = 200/1, flow rate = 1.0 mL/min). *t*_R = 46.85 min (minor), *t*_R = 95.00 min (major) (*syn*), *t*_R = 42.46 min (minor), *t*_R = 56.03 min (major) (*anti*).

3-Hydroxy-2-methyl-1-phenyl-1-undecanone: (*syn/anti* = 61/39)

syn:

¹H NMR (CDCl₃) δ 0.80-0.85 (m, 4H), 1.19-1.17 (m, 16H), 3.08 (brs, 1H), 3.38-3.45 (m, 1H), 3.96-3.99 (m, 1H), 7.41-7.45 (m, 2H), 7.51-7.55 (m, 1H), 7.88-7.91 (m, 2H).

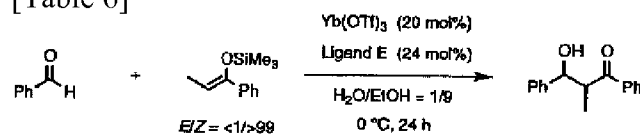
¹³C NMR (CDCl₃) δ 11.0, 14.0, 22.6, 26.1, 29.2, 29.5, 29.6, 31.8, 34.3, 34.8, 44.4, 71.3, 120.7, 128.3, 133.4, 135.9, 205.9.

HPLC (Daicel Chiralcel AS, hexane/*i*-PrOH = 90/1, flow rate = 1.0 mL/min). *t*_R = 10.52 min (minor), *t*_R = 15.11 min (major) (*syn*), *t*_R = 11.56 min (minor), *t*_R = 34.22 min (major) (*anti*).

[0041] In <Example 3> example 1, the reactional solvent was changed and the reaction as the following table was performed. The result was shown in the table.

[0042]

[Table 6]



Run	Solvent	Yield (%)	Syn/Anti	Ee (Syn/Anti)
1	H ₂ O/THF = 1/9	77	68/32	22/4
2	H ₂ O/EtOH = 1/9	69	73/27	32/4
3	H ₂ O/ <i>i</i> PrOH = 1/9	43	71/29	33/7
4	H ₂ O/EtOH = 1/3	92	76/24	30/2
5	H ₂ O/EtOH = 1/27	47	76/24	30/2

[0043] An aldehyde compound is replaced with CH₃-(CH₂)₆-CH₂-CHO in <Example 4> example 1, The dissymmetry aldol reaction was performed about the case where each of Y(OTf)₃ and Dy(OTf)₃ is used as a rare earth metal compound.

[0044] As a result, in Y(OTf)₃, the 3-hydroxy-2-methyl-1-phenyl-1-undecanone of output was Syn/anti=59/41, and was Syn=41%ee. In Dy(OTf)₃, they were Syn/anti=57/43, and syn=39%ee. In <Example 5> example 1, it reacted using the compound which set to -CH₂-OTBS -CH₂-OH combined with the oxazoline ring of the chiral pyridinescrew oxazoline compound of a ligand.

[0045]As a result, 53% of yield, syn/anti=62/38, syn = the result of ee was obtained 18%.

[0046]

[Effect of the Invention]Yield and optical selectivity are also high and the new asymmetric-synthesis catalyst whose reaction operation in simple and mild conditions it is flexible and is moreover made possible, and the asymmetric synthesis method using this are provided by the invention of this application as explained in detail above.